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Gene Section
Review

PIM1 (pim-1 oncogene)

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Identity

Other names: PIM

HGNC (Hugo): PIM1

Location: 6p21.2

DNA/RNA

Description

PIM1 is a single gene with 5 introns and 6 exons that span 5 kb of DNA in the human genome (Meeker et al., 1987).
The gene starts at 37137922 and ends at 37143204 base pairs from pter. It is highly conserved evolutionarily across species.

Transcription

The mRNA sequence is 2,6 kb in length with a 941 bp coding region.

Protein

Description

Size: 313 amino acids; molecular weight: 36 kDa.
The PIM1 gene has six exons, but there are two isoforms of PIM1 protein, 34 kDa and 44 kDa, due to protein synthesis using alternative sites of translation initiation (Saris et al., 1991).
Both proteins show comparable kinase activities in vitro, but the 44 kDa isoform contains an N-terminal proline-rich motif that binds the ETK SH3 domain, and is recruited to the plasma membrane (Xie et al., 2006).

Expression

The kinase activity of all the PIM proteins is constitutively active, and there are no regulatory domains in the amino acid sequences of the PIM proteins.
Thus, unlike other kinases that are regulated by phosphorylation or binding to the plasma membrane, the activity of PIM1 is regulated primarily by transcription, translation and proteosomal degradation (Amaravadi and Thompson, 2005).
The gene expression of PIM1 is increased by various cytokines, mitogens and hormones such as G-CSF, GM-CSF, erythropoietin, interleukins, Con A, PMA, interferons, and prolactin (Wang et al., 2001; Hogan et al., 2008; White, 2003).
These factors act through the JAK/STAT pathway. The upregulation of PIM1 gene expression results from the binding site of STAT3 or STAT5 to the PIM1 gene promoter, and the ISFR/GAS-sequence (IFN-γ activation sequence) is an important binding site (Block et al., 2012; Matikainen et al., 1999; Yip-Schneider et al., 1995).
PIM1 phosphorylates and stabilizes SOCS proteins (suppressor of cytokine signaling) to provide negative feedback regulation of the JAK/STAT pathway (Peltola et al., 2004).
NF-κB, as a downstream transcription factors, could also activate PIM1. In solid tumors, hypoxia would induce the PIM1 expression, independently of HIF1α and by Krueppel-like factor 5 (KLF5) upon DNA damage (Chen et al., 2009a). ERG, as a transcription factors, also plays a role in PIM1 expression in the initial stages of prostate carcinogenesis (Magistroni et al., 2011).

Because of multiple copies of AUUU(A) motifs in the 3'UTR and GC-rich regions in the 5'UTR, mRNA of PIM genes are short lived (Wang et al., 2005).
Translation of PIM1 seems to be cap-dependent, and overexpression of elF4E would increase PIM1 protein level (Hoover et al., 1997).
PIM RNA transcripts are regulatory targets of different miRNAs such as microRNAs miR1, miR-210, miR-33a, and miR328, implicating another layer of PIM expression regulation (Eiring et al., 2010; Huang et al., 2009; Nasser et al., 2008; Thomas et al., 2012).
At the post-translational level, the short half-life of PIM1 is primarily regulated by proteasomal degradation. PIM1 protein can be stabilized by the binding to HSP90 (Mizuno et al., 2001).
On the other hand, binding to HSP70 would induce the ubiquitylation of PIM1 and proteasomal degradation (Shay et al., 2005).
Also, in hypoxia, ubiquitin-mediated proteasomal degradation of PIM is prevented by HSP90 (Mizuno et al., 2001). PIM1 protein stability is further regulated by its phosphorylation status. PIM1 is able to autophosphorylate (Bullock et al., 2005). Phosphorylation by itself and/or other unknown kinases is important for PIM1 protein stability and function because PP2A phosphatase negatively regulates PIM1 stability (Losman et al., 2003).

Localisation

PIM1 is highly expressed in lymphoid and hematopoietic tissues (bone marrow, thymus, spleen, and fetal liver) (Eichmann et al., 2000) as well as in some non-hematopoietic tissues (e.g., hippocampus, oral epithelium, and the prostate gland). In some myeloid and lymphoid leukemia cell lines, prostate cancer cell lines, and also HeLa cells, PIM have also been detected. The PIM1 protein can be detected subcellularly in the cytoplasm and the nucleus.

Function

PIM1 phosphorylates a large subset of cellular substrates and thus regulates many different cellular processes such as cell cycle progression, cellular division, differentiation and apoptosis.
One of the cell-cycle-related targets of PIM1 is $p21^{waf1}$ (Wang et al., 2002; Zhang et al., 2007). By phosphorylating the CDK inhibitor $p21^{waf1}$ on T145, PIM1 lead to the nuclear export and inactivation of $p21^{waf1}$. Phosphorylation of another CDK inhibitor $p27^{Kip1}$ at Thr157 and Thr198 would induce its proteasomal degradation and cell cycle progression.
Moreover, PIM1 seems to phosphorylate and inactivate the transcription factors of $p27^{Kip1}$,
FoxO1a and FoxO3a (Morishita et al., 2008). Another mechanism of $p27^{Kip1}$ regulation is the phosphorylation of SKP2 at Thr417, which control its stability and ability to degrade p27 (Cen et al., 2010). Additionally, the phosphorylation of Cdc25A and Cdc25C would induce G1/S and G2/M transition, respectively (Bachmann et al., 2004).
PIM1 also implicate in mitosis promotion by interacts with dynein/dynactin and HP1β (Magnuson et al., 2010).
Moreover, PIM1 is involved in genomic instability. By interaction with NuMA (nuclear mitotic apparatus protein), overexpression of PIM1 causes the loss of checkpoint control (Bhattacharya et al., 2002).
Consequently, cells with abnormal mitotic spindles are not arrested in mitosis, producing polyploid and multinucleated daughter cells.
PIM1 can also act as an oncogenic survival factor because of its function in blocking apoptotic cell death.
It is consensus that phosphorylation of BAD at S112 would induce its proteasomal degradation and thus shifts the apoptosis threshold (Peltola et al., 2004).
The proapoptotic activity of ASK1 and PRAS40 would also be impaired by PIM1 phosphorylation (Gu et al., 2009; Zhang et al., 2009).
Through inactivation of ASK1 and subsequently less phosphorylation of the stress kinases JNK and p38, caspase-3 activation would be less and thus reduce cell death.
Moreover, the block of MDM2 and p53 degradation by PIM1 may induce senescence in embryonic fibroblasts and cancer cells (Hogan et al., 2008).
When bound to MYC at the E-box, PIM1 would participate in the complex's phosphorylation of histone H3 at S10 and thus participate in the stimulation of transcription of a specific subset of MYC-dependent genes (Zippo et al., 2007).
Additionally, PIM1 influences the activity of a number of transcriptional regulators, such as HP-1, PAP-1, TFAF2/SNX6, NFATc1, p100, RUNX, SOCS1, RelA/p65 and c-Myb (Bhattacharya et al., 2002; Evans and Fox, 2007; Ishibashi et al., 2001; Kim et al., 2010; Rainio et al., 2002; Winn et al., 2003).
PIM kinases also phosphorylate 4E-BP1, inhibiting its binding to elF-4E.
Since elF-4E is a rate-limiting factor in protein synthesis, PIM kinases may also regulate 5' cap-dependent translation (Beharry et al., 2011).

Implicated in

t(3;6)(q27;p21.2) in diffuse large B-cell lymphoma (DLCL); chimeric BCL6 / PIM1

Note
Only 1 case to date.

Hybrid/Mutated gene
5' PIM1 fused to 3' BCL6; the substitution of the promoter of BCL6 causes deregulation of BCL6.

Myeloid and lymphoid leukemias and other lymphomas

Oncogenesis

PIM1 induces anti-apoptotic oncogenes such as BCR/ABL, FLT2, CBL or JAK2 (Adam et al., 2006; Mizuki et al., 2003; Naramura et al., 2011; Nieborowska-Skorska et al., 2002; Wernig et al., 2008). PIM1 mRNA is upregulated in acute myeloid leukemia (AML) along with MLL gene rearrangements, e.g., MLL/AF9 or MLL/ENL (Chen et al., 2008). The reason for PIM1 levels increase seems to be the constitutive activation of FLT3 or Hoxa9 (Hu et al., 2007). Additionally, PIM1 also involve in the several B-cell developmental disorders that are related to Kaposi sarcoma associated herpesvirus (KSHV) or the Epstein-Barr virus (EBV) (Bajaj et al., 2006; Cheng et al., 2009).

Prostate cancer

Prognosis

In more half of the prostate cancer samples, PIM1 is showed a relatively overexpression compared to benign lesions and the expression elevation correlated with a poor therapeutic outcome (Dhanasekaran et al., 2001).

Oncogenesis

In mouse model, the synergistic effects of PIM1 and MYC showed obvious co-regulation in prostate cancer. The molecular mechanism for the oncogenic activity might because PIM1 phosphorylation of c-MYC would increase its half-life and also because PIM1 enhancement of transcriptional activity of c-MYC (Chen et al., 2009b; Mumenthaler et al., 2009). Moreover, PIM1 kinase is related to chemoresistance in prostate cancer cells, which is related to relatively aggressive or hormone-refractory prostate cancers. The high level of expression of PIM1 in high grade prostate intraepithelial neoplasia may indicate a role of PIM1 in the early prostate carcinogenesis. PIM1 is also found to be upregulated in patients undergoing androgen ablation therapy (van der Poel et al., 2010).

Pancreatic cancer

Note

Hypoxia-promoted genetic instability

Oncogenesis

PIM1 increases in hypoxic condition, independently of HIF-1α (Reiser-Erkan et al., 2008). It is now proposed as a prognostic marker. Increase in PIM1 expression may partly account for resistance to chemotherapy.

Sporadic malignant tumors

Oncogenesis

Overexpression of PIM1 is founded in gastric carcinoma, squamous cell carcinoma, colorectal carcinoma, liver carcinoma (Shah et al., 2008), liposarcoma (Nga et al., 2010), and bladder cancer (Guo et al., 2010).

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